REMARKS

As an initial matter, Applicant wishes to thank Examiner Fubara for the courtesy of an interview extended Applicant's undersigned representative on October 6, 2009.

Status of the Claims

Claims 34-42 and 62-76 remain pending herein.

The claims have been amended to further clarify that that the microparticle composition described is a microparticle suspension, support for which can be found, for example, in Examples 5-7. Support for not subjecting the microparticle suspension to a step to remove excess detergent can be found, for example, in paragraph [0025]. See also claim 40. Support for mixing a biologically active macromolecule with the microparticle suspension to achieve adsorption can be found, for example, paragraphs [0100] and [0127].

Hence no new matter has been added.

Prior Rejections under 35 U.S.C. 102(a) and 103(a)

Applicant notes, with thanks, the Examiner's withdrawal of various prior claim rejections under 35 U.S.C. 102(a) and 103(a).

Claim Rejections under 35 U.S.C. 112, first and second paragraphs

Claim 70 is rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement and under 35 USC 112, second paragraph as indefinite.

This rejection is moot in view of the above amendment of claim 70.

Reconsideration and withdrawal of the rejections under 35 U.S.C. 112, first and second paragraphs are thus requested.

Claim Rejection under 35 U.S.C. 103-Levy in view of O'Hagan and Van Nest

Claims 34-42 and 62-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,395,253 to Levy et al. (Levy) in view of O'Hagan et al., WO 00/50006 (O'Hagan) and Van Nest, US Pub. No. 2001/0046967 (Van Nest). Applicant respectfully traverses this rejection and its supporting remarks.

For a proper obviousness rejection, the differences between the subject matter sought to be patented and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. §103. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. MPEP 2141. " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007), quoting *In re Kahn ,* 441 F.3d 977, 988, (Fed. Cir. 2006). Moreover, the prior art reference (or references when combined) must teach or suggest all the claimed features. "When determining whether a claim is obvious, an examiner must make 'a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.' … Thus, 'obviousness requires a suggestion of all limitations in a claim.' …" *Ex parte Wada and Murphy*, BPAI Appeal No. 2007-3733, January 14, 2008 (emphasis in original) (citations omitted). In addition, there must be a reasonable expectation of success. See MPEP 2143.02.

All claims require processes whereby macromolecules are adsorbed to microparticle suspensions that contain bound and unbound detergent. Levy, on the other hand, does not teach or suggest adsorption to microparticles, but rather is directed to improved methods for *incorporating* nucleic acids *into* polymeric microspheres and/or nanospheres (micro-encapsulation) through the use of a condensing agent. See, e.g., Abstract. See also the title of Levy: Microspheres *Containing* Condensed Polyanionic Bioactive Agents and Methods for Their Production. See further the generic microsphere preparation method in Levy, Section 4.2, which states that the microspheres formed contain the bioactive agent:

> In the standard embodiment … at least one biocompatible biodegradable polymer is dissolved in a water-immiscible organic solvent to yield an organic phase. The hydrophilic bioactive agent [nucleic acid] is dissolved in water to yield a first aqueous phase, and the two phases are then emulsified to yield a water-in-oil (W/O) emulsion. A second aqueous phase is then formed… The W/O emulsion and the second aqueous phase are again emulsified to yield a double water-in-oil-in-water (W/O/W) emulsion. The organic solvent is then removed from the W/O/W emulsion, *yielding microspheres containing the hydrophilic bioactive agent*….

In all presently pending claims, on the other hand, a biologically active macromolecule is mixed with the microparticle suspension, resulting in the adsorption of the biologically active macromolecule to microparticles in said suspension.

Thus the teachings of Levy are not relevant to the pending claims and do not include the elements of the pending claims.

The Examiner has responded by urging that "incubating or bringing together … [or] contacting of the biological molecule with the microparticles in Levy should also result in adsorption of the biological molecules except [where] applicant shows that the biologically active agents in Levy are not adsorbed and except [where] there are other steps of adsorbing biomolecules to particles that applicant has not claimed … [or] disclosed that would prove superior to the contacting or incubation step described in applicants specification. The burden was on the applicant to factually show that the bio-molecules of Levy are not bound to the microparticles … 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.'…"

However, there is no reason for one of ordinary skill in the art to go about "incubating or bringing together … [or] contacting of the biological molecule with the microparticles in Levy". More particularly, as noted above, Levy is directed to improved methods for *incorporating* nucleic acids *into* polymeric microspheres and/or nanospheres (micro-encapsulation) through the use of a condensing agent. Hence, one of ordinary skill in the art would have no reason to perform the operation suggested by the Examiner.

The presently pending claims are *method* claims in which a biologically active macromolecule is *adsorbed* to a previously formed microparticle composition containing bound an unbound detergent. In the method of Levy, on the other hand, the macromolecule (DNA) is positioned in the inner phase of a double water-in-oil-in-water (W/O/W) emulsion. Organic solvent is then removed from the W/O/W emulsion, yielding microspheres that contain the encapsulated macromolecule. Thus, the macromolecule is introduced to the Levy composition prior to microparticle formation, whereas in the present invention it is introduced after microparticle formation. Moreover, the macromolecule is encapsulated in the Levy microparticles, whereas in the present invention it is adsorbed to the microparticles.

Furthermore, all presently pending independent claims concern microparticle compositions in which macromolecules are adsorbed to microparticles in a microparticle composition in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. As explained in the present specification at

paragraph [0011] onwards, the inventors have unexpectedly found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This feature of the invention is neither taught nor suggested by the prior art, including Levy.

In some embodiments, a microparticle suspension (formed by removing organic solvent from an emulsion comprising polymer, organic solvent, detergent and water) is subjected to a filtration step to remove excess detergent such that about 10-90% of the total detergent in the resulting microparticle suspension is bound to the microparticles and the remainder is unbound.

In other embodiments a microparticle suspension in which 10-90% of the total detergent is bound to the microparticles and the remainder is unbound is achieved without performing a detergent removal step.

Applicant had previously claimed that the microparticle suspension was not subjected to a washing step in some embodiments, and the Examiner had argued that "while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation…" The pertinent portion of Section 4.2 of Levy, at col. 6, lines 42-57, reads as follows (emphasis added):

> In the standard embodiment of the water-in-oil-in-water double emulsion protocol for making microspheres containing hydrophilic bioactive agents (including polyanionic bioactive agents), at least one biocompatible biodegradable polymer is dissolved in a water-immiscible organic solvent to yield ***an organic phase***. The hydrophilic bioactive agent is dissolved in water to yield a ***first aqueous phase***, and the two phases are then emulsified to yield a water-in-oil (W/O) emulsion. A ***second aqueous phase*** is then formed, optionally including an emulsifying agent that facilitates the formation of an emulsion. The W/O emulsion and the second aqueous phase are again emulsified to yield a double water-in-oil-in-water (W/O/W) emulsion. The organic solvent is then removed from the W/O/W emulsion, yielding microspheres containing the hydrophilic bioactive agent. ***The microspheres are recovered by ultracentrifugation.***

First, it should be noted that the microsphere suspension in Levy (which is created by removing the organic solvent) is ***not*** subjected to a filtration step to remove excess detergent as claimed in certain embodiments of the invention.

In other embodiments of the invention, the microparticle suspension is not subjected to a step to remove excess detergent. The microsphere suspension in Levy, on the other hand, is subjected to an ultracentrifugation step whereby particles are recovered. Such a step would constitute a detergent removal step and would thus be excluded by the present claims.

With regard to the requirement of a microparticle suspension in which 10-90% of the total detergent is bound to the microparticles and the remainder is unbound, Levy does not teach or suggest such a composition.

Nor is such a composition inherent in the teachings of Levy. For example, in the above description, the emulsifying agent (detergent) is *optional*. Thus, the amount of detergent in Levy can be very low, and indeed can be zero, necessarily leading to a composition in which there is no bound and unbound detergent. On the other hand, volumes and concentrations for the organic phase (which contains the polymer) and the second aqueous phase (which contains the optional emulsifying agent) may be selected which would yield a composition with greater than 90% unbound detergent (e.g., by providing a large amount of emulsifying agent relative to the polymer).[1] Thus, while it may be *possible* to select volumes and concentrations for the organic and aqueous phases in Levy which would result in a microparticle suspension in which 10-90% of the total detergent is bound to the microparticles and the remainder is unbound (as Applicant has done, for example, as described in paragraph [0028] and Example 6), such a result is not assured.

In this regard, see, for example, the following excerpt from MPEP 2112.IV (emphasis in original) (citations omitted):

> The fact that a certain result or characteristic <u>may</u> occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic…."To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "…

In addition to Section 4.2 of Levy discussed above, the Office Action also refers to the Alternative Protocols described in Section 4.6 of Levy:

> In alternative embodiments, microspheres may be prepared using protocols commonly employed in the art. These protocols include, but are not limited to, the phase-separation or coacervation protocol, described in Wantier et al., U.S. Pat. No. 5,478,564; the single-emulsion protocol, described in Jaffe, U.S. Pat. No. 4,272,398; the salting out protocol, described in Allemann et al., 1992, Intl. J. Pharmaceutics 87:247-253; the diafiltration method, described in Maruyama et al., 1997, Bioconjugate Chem. 8:735-42; and the hot melt, solvent removal, spray drying, double walled microsphere, and hydrogel protocols, all described in Mathiowitz et al., WO95/24929 (pages 10-13). The disclosures of the above references are hereby incorporated by reference in their entireties.

[1] In the present invention, such a circumstance may be dealt with by employing a filtration step to remove excess detergent, however, such a step is not taught by Levy.

However, this portion of Levy is even further removed from the claimed invention than is Section 4.2 discussed above.

As in prior Office Actions, the Examiner again argues that "Levy uses 0.1% detergent (SDS in this case)." As previously noted, it is true that Levy discloses SDS (an anionic detergent) in Section 5.3.2. However, this is part of Section 5.3 (Characterization of Condensed DNA Microspheres), and SDS is used in Section 5.3.2 as an *analytical reagent* to assess previously formed microspheres (emphasis added): "*Dissolution studies* were carried out by incubating samples of DNA-containing microspheres in an excess of TE buffer with and without 0.1% sodium dodecyl sulfate (SDS)." Thus, the disclosure is not relevant to the claimed invention.

In an attempt to justify the use of the SDS disclosure in Levy, the Examiner references the case law cited in MPEP 2144.04, specifically *Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.), *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results), and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

What the Examiner is proposing, however, is *not* changing the order of steps within a given process. Rather, the Examiner is proposing taking a step from one process (i.e., an analytical process) and inserting it into another unrelated process (i.e., an emulsification process) without any reason or justification for doing so.

The Examiner also states: "There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles." However, it is noted that no unusual/unexpected results are required as no *prima facie* case of obviousness has been made (although Applicant has provided unexpected results as discussed further below).

The Examiner further argues that "[t]he claims do not recite amount of detergent added to make the microparticle in the emulsion." Such amounts are recited in independent claims 37 and 39. With regard to independent claim 34, this amount is an amount of detergent which, after performing the methods steps of the claims, provides a microparticle suspension in which about

10-90% of the total detergent in the microparticle suspension is bound to the microparticles and the remainder is unbound. As described in the specification, such an amount will vary depending, for example, on whether the microparticle suspension is subjected to a filtration step to remove detergent or whether the microparticle suspension is not subjected to a detergent removal step.

With regard to filtration, including the cross-flow filtration recited in claim 36, the Examiner has taken the position that filtration "appears to be equivalent to washing" and that "filtration is a form of washing". Consequently, the Examiner urges that the filtration steps of claims 34 and 36 read on the wash step of one of the embodiments of Levy at col. 13, line 5 (microspheres washed one or more times with water, Tris-EDTA, etc.), at col. 18, line 42 (washed three times with Tris-EDTA) and at col. 20, line 2 (this section reads on washing living *cells*, rather than microspheres).

The Hawley's Condensed Dictionary entry previously cited by Applicant describes "filtration" as "[t]he operation of separating suspended solids from a liquid (or gas) by forcing the mixture through a porous barrier …" Because "filtration" requires the use of a porous barrier (i.e., a *filter*), filtration is neither taught nor suggested by the washing steps Levy. In this regard it is noted that the claims at issue are method claims. A filtration process is not rendered obvious by the disclosure of a washing step, even assuming solely for the sake of argument that both process might somehow be used to produce microparticle suspensions having similar amounts of bound and unbound detergent. Among other requirements, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the limitations of the claims.

Note also that the claims presently make clear that, in the claimed filtration step, a *suspension* is subjected to a filtration step to remove excess detergent and produce a *suspension* which contains the claimed amount of bound and unbound detergent.

In this regard, as seen in the introductory materials previously attached to Applicant's Office Action response dated May 1, 2006, cross-flow filtration (CFF), also known as Tangential Flow Filtration (TFF), is a process wherein a feed stream passes parallel to a membrane face, with a portion of the stream passing through the membrane (permeate) while the remainder (retentate) is recirculated back to a feed reservoir. An advantage of cross-flow filtration is that smaller species (e.g., detergent) can be separated from a larger species (e.g., microparticles). Unlike some filtration processes in which the result is a filter cake, with cross-flow filtration a detergent-containing suspension can be used as a feed stream with the resulting retentate also being in the

form of a suspension, albeit with a portion of the detergent being removed. In this regard, see, for example, Example 5 of the specification, in which a suspension in accordance with the claimed invention is collected after removing excess CTAB. There isn't the remotest resemblance between such a process and the washing step of Levy.

With regard to claims 68-70, the Examiner also argues that, in one of the embodiments, Levy does not wash the product so that the detergent is not removed or washed off (column 12, lines 58-67). It is further argued by the Examiner that, while Levy does not specifically state the presence of bound detergent in the amounts recited in the claims, Levy does not specifically state that the microspheres/particles formed are free of detergent; and it follows from one of the embodiment that does not use a wash step but evaporates off the organic solvent (column 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated.

As noted above, however, Levy does not teach or suggest a microparticle suspension in which 10-90% of the total detergent is bound to the microparticles and the remainder is unbound. Nor is such a microparticle suspension inherent in the teachings of Levy. For example, in the portion of Levy spanning columns 11 and 12, the microparticles are optionally washed one or more times. Thus, the microparticles may or may not be washed. Applicant had previously noted that absent a reason to ensure that unbound detergent remains in the microparticles, one of ordinary would be motivated to wash the microparticles of excess detergent by centrifugation as taught by Levy. Applicant had also cited Singh et al., *Proc. Natl. Acad. Sci. USA*, 2000, 97:811-816 (of record—see the IDS filed 2/10/04), page 815, right column, third paragraph, as showing that there is motivation in the art to keep detergent levels, particularly cationic detergent levels, to a minimum. Although not used in the current rejection, Singh et al. nonetheless constitutes evidence of the motivations of those of ordinary skill in the art with regard to washing. Indeed, the microparticles were washed three times in the Examples of Levy. As indicated in paragraph [0011] of the present specification, such washing steps remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles.

Moreover, as previously noted, even assuming solely for the sake of argument that the particles are not washed, the emulsifying agent (detergent) is *optional*. Thus, the amount of detergent in Levy can be very low, and indeed can be zero, necessarily leading to a composition in

which there is no bound and unbound detergent. Furthermore, even assuming for the sake of argument that a second aqueous phase having an emulsifying agent concentration of about 0.05% to about 10% (see col. 12, line 57) is employed, volumes and concentrations for the organic phase (which contains the polymer) and volumes for the second aqueous phase (which contains the emulsifying agent) may be selected which would yield a composition with greater than 90% unbound detergent (e.g., by providing a large amount of emulsifying agent relative to the polymer).[2] As noted above: "Inherency … may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

The Examiner has argued: "The artisan must determine that the amount of bound and unbound detergent and applicant has not determined that either less than 10-90% detergent is bound to the microparticles in the Levy art or that less than 10-90% is unbound of the total detergent in the microparticles." Absent a disclosure of the volumes and concentrations for the organic phase (which contains the polymer) and volumes for the second aqueous phase (which contains the optional emulsifying agent), however, there is nothing for the artisan to "determine." Applicant has shown that the process of Levy need not produce a microparticle suspension with the amounts of bound and unbound detergent claimed. Thus, such amounts are not inherent in Levy.

Moreover, as previously indicated, even assuming *solely* for the sake of argument that, at some point in the process described by Levy, a microparticle composition exists in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound, Levy nonetheless does not provide the basis for a proper *prima facie* rejection. This is true at least because the presently pending claims are *method* claims in which a biologically active macromolecule is mixed with a microparticle suspension in which about 10-90% of the total detergent in the microparticle suspension is bound to the microparticles and the remainder is unbound such that said biologically active macromolecule is adsorbed to microparticles in the suspension. Thus, in the present invention the macromolecule is introduced *after* microparticle formation, whereas in Levy the macromolecule is introduced *prior to* microparticle formation (as the inner phase of a W/O/W emulsion). Moreover, the macromolecule in the present invention is *adsorbed* to the microparticles, whereas the macromolecule in Levy is

[2] In the present invention, such a circumstance may be dealt with by employing a filtration step to remove excess detergent, however, such a step is not taught by Levy.

encapsulated in the microparticles. Levy cannot possibly be said to teach or suggest adsorbing a biologically active macromolecule to microparticles in a microparticle composition in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound, at least because Levy does not teach contacting a biologically active macromolecule with microparticles at all.

O'Hagan is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion with macromolecules, and Van Nest relied upon for teaching that polynucleotides may be delivered in vehicles such as liposomes or emulsions made with cationic lipids or polymers, such as 1,2-dioleoyl- l,2,3-trimethylammoniopropane (DOTAP), cetyltrimethylammonium bromide (CTAB) or polylysine. Such teachings, however, do not make up for the above noted deficiencies in Levy.

For at least the above reasons, it is respectfully submitted that Levy does not support a *prima facie* case of obviousness against claims 34-44 and 58-76.

The Examiner further argues that there is no demonstration in Applicant's specification that not subjecting microparticles to a washing step or subjecting them to a cross-filtration step provides unusual/unexpected properties.

As explained in the present specification at paragraph [0011] onwards, the inventors have found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished in several ways, including filtration and the avoidance of a washing step. Such a result is entirely unexpected in view of the prior art and constitutes objective evidence of the non-obviousness of the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966).

For example, O'Hagan, in Example 7 and Table 4 disclose results of loading pCMVgp120 plasmid DNA onto washed PLG-CTAB particles. For a theoretical load of 1%, the actual load was 0.84%, or a loading efficiency of 84%. Table 4 also discloses loading pCMVgp120 plasmid DNA onto washed PLG-PVA particles. For a theoretical load of 1%, the actual load was 0.44%, or a loading efficiency of 44%.

Example 4 of the present specification discloses the results of loading a complex of pCMVp55gag plasmid DNA and CTAB onto washed PLG-PVA microparticles. The theoretical

load was 1%, whereas the actual load was 0.91%, or a loading efficiency of 91%. The loading efficiency onto PLG-PVA particles in Example 7 of O'Hagan, by contrast, is 44%.

Example 7 of the present specification discloses results of loading pCMVp55gag plasmid DNA onto non-washed PLG-CTAB microparticles prepared in Example 6. The theoretical load was 1%, whereas the actual load was about 1%, or a loading efficiency of about 100%. By contrast, the loading efficiency onto PLG-CTAB particles in Example 7 of O'Hagan is 84%.

With regard to the data of Example 7 of the present specification, it is respectfully submitted that one of ordinary skill in the art would have expected the unbound CTAB detergent to interfere with DNA loading onto the PLG-CTAB particles (Example 4 concerns PLG-PVA particles). More particularly, the positive charge of the unbound CTAB would be expected to associate with the negatively charged backbone of the DNA. This, in turn, would be expected to shield the overall negative charge of the DNA, such that it would be less attracted to the positively charged CTAB that is bound to the microparticles. Contrary to that expectation, the presence of unbound CTAB actually increases loading efficiency. Washing away the unbound CTAB as was done in O'Hagan, on the other hand, does *not* improve loading efficiency, but actually reduces loading efficiency.

For at least the above reasons, withdrawal of the rejection of the claims over Levy in view of O'Hagan and Van Nest is requested.

CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

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